UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,821	10/16/2003	Eric Wickstrom	W1133/20008	2530

3000 7590 11/14/2006

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.
11TH FLOOR, SEVEN PENN CENTER
1635 MARKET STREET
PHILADELPHIA, PA 19103-2212

EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,821	WICKSTROM ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-75,80,82,83 and 85-88* is/are pending in the application.

4a) Of the above claim(s) *5,6,15,17-25,35-40,46,47,53,57-68,74 ~~and 84~~* is/are withdrawn from consideration. J.E

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-14,16,26-34,41-45,48-52,54-56,69-73,75,80,82,83,85,86 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 2, 76-79, 81,and 84 have been cancelled. Claims 1, 3, 54, 69, 80, 82, and 85 have been amended. Claim 88 is new. No new matter was introduced by these amendments or by the new claim 88. Claims 5, 6,15, 17-25, 35-40, 46, 47, 53, 57-68, 74, and 84 have been withdrawn.

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82, 83,85, 86, and 88 are under examination.

Response to Arguments

Claim Objections

3. The objections to claims 69-73, 75, and 84 are withdrawn in response to Applicants' amendments to the claims filed on 08/28/2006.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The rejections of claims 76-82 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps and for being indefinite is withdrawn in response to Applicants' amendment to claim 80 and 82 and cancellation of claims 76-79 and 81 on 08/28/2006.

Claim Rejections - 35 USC § 102

5. The rejection of claims 1-4, 28-32, 34, 69, 71-73, 76, 80, 81, 83, 85, and 86 under 35 U.S.C. 102 (b) as being anticipated by Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180), as evidenced by Basu et al. (Bioconjugate Chem, 1997, 8: 481-488) is withdrawn in response to cancellation of claims 2, 76, and 81, and in response to Applicant's amendments to the claims filed on 08/28/2006.

6. The rejection of claim 1, 2, 4, 7-10, 12-16, 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 under 35 U.S.C. 102 (b) as being anticipated by Tomalia et al. (US Patent No. 5,714,166), as evidenced by Basu et al. is withdrawn in response to cancellation of claim 2, and in response to Applicant's amendments to the claims filed on 08/28/2006.

Claim Rejections - 35 USC § 103

7. The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., in view of Meade et al. (US Patent No. 6,713,046) is withdrawn in response to cancellation of claim 2 on 08/28/2006.

8. The rejection of claims 1-4, 28-32, 34, 69, 71-73, 76-81, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Basu et al., in view of Tomalia et al. is withdrawn in response to cancellation of claims 2,

76-79, and 8, and in response to Applicant's amendments to the claims filed on 08/28/2006.

9. Claims 1, 4, ~~7-16~~ 7-14, 16 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 remain and the new claim 88 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., as applied to claims 1, 2, 4, 7-10, ~~12-16~~ 12-14, 16 26-28, 34, 41-45, 48, 49, 52, 54-56, 69, 70, 73, 75, 83, 85, and 86 above, in view of Meade et al. (US Patent No. 6,713,046), for the reasons of record set forth in the prior Office Action. Applicant's arguments filed 08/28/2006 have been fully considered but they are not persuasive. 9.E.

Applicants traversed the instant rejection on the grounds that the amendment to the base claim 1 obviates the rejection because none of the above references teach or suggest a compound comprising a dendrimer (X) covalently linked to a PNA (P), which in turn is covalently linked to a targeting moiety (T), wherein the compound is represented by the formula X-L1-P-L2-T and wherein L1 and L2 represent at least one linking moiety. Applicants argues that Tomalia et al. do not suggest to modify their compound to yield the instant invention and therefore, the reference would not have motivated one of skill in the art to make the claimed invention because it teaches that the genetic material can be complexed with a dendrimer only via a non-covalent association (column 47, lines 55-62). For these reasons, Applicants argue, one of skill in the art would have lacked motivation to use the teachings of Tomalia et al. alone or in

combination with the teachings of the secondary reference to make the composition of the instant invention with a reasonable expectation of success.

Contrary to Applicants' assertions, the base claim 1 does not recite a covalent bond. Claim 1 recites a therapeutic moiety that is "conjugated" to a PNA and a targeting molecule. Conjugation means joining two or more compounds, regardless of the nature of the bond between the compounds, i.e., a conjugate can be obtained by using non-covalent bonds (see also the definition at dictionary.com). Moreover, Applicant's statement that Tomalia et al. teach only non-covalent association between the genetic material and the dendrimer is not accurate. Tomalia et al. teach a compound with the formula T-L1-P-L2-M, wherein M represents a PNA, T represents a targeting moiety that can bind a cell-surface molecule, P represents a dendrimer, and wherein M and T are associated with P via identical or different linkers, L1 and L2 (column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47,lines 1-10, column 52, lines 57-60). It is noted that Tomalia et al. teach that "associated with" means that the material is either physically dispersed throughout the dendrimer or linked to the dendrimer, wherein linkage is by means of covalent bonding (column 17, lies 41-67). Therefore, even if in a particular embodiment they teach a complex between the genetic material and the dendrimer wherein the formation of the complex does not take place via covalent bonding (column 47, lines 55-62), Tomalia et al. do teach other embodiments wherein the genetic material and the dendrimer are linked by covalent bonds. Tomalia et al. teach a compound with the formula T-L1-P-L2-M, wherein P and M are the equivalents of X and P of the instant claims, i.e., they teach a compound with

the formula T-L1-X-L2-P. Therefore, Tomalia et al. do not teach the specific arrangement recited in the instant claims, i.e., X-L1-P-L2-T. However, as stated above, Tomalia et al. teach all components necessary for this arrangement. It is noted that there is no evidence on the record that the claimed arrangements result in a compound exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum control of targeted delivery to a particular cell/site. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. In conclusion, the instant invention was *prima facie* obvious at the time the invention was made.

New rejections

Claim Objections

10. Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48-52, 54-56, 69-73, 75, 80, 82, 83, 85, 86, and 88 are objected to because of the following informalities: the instant claims recite a targeting moiety capable of binding a cell surface molecule and the redundant recitation of the targeting moiety being bound by a cell surface molecule. Appropriate correction to remove the redundant recitation is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (2002, cited on form PTO-892 on 05/16/2006), in view of Liang et al. (Molecular Therqapy, 2000, 3: 236-243), as evidenced by Basu et al. (1997, cited on form PTO-892 on 05/16/2006).

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a radiometal (i.e., a polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, is further coupled to a peptide designated for intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety); the targeting peptide and DOTA are conjugated to PNA via linkers (claims 1, 3, 4, 29, 34, 83, 85, and 86) (Abstract, p. 1177, Fig. 1). Lewis et al. teach contacting cells known to comprise high and low levels of *bcl-2* with the DOTA-PNA-peptide conjugate, allowing for the conjugate to be internalized by the cells, and detecting the conjugate within the cells to determine the level of expression of *bcl-2* transcript (claims 1, 30-32, 69, and 71-73). Lewis et al. teach that cells expressing high levels of *bcl-2* internalize significantly more conjugate as compared to cells expressing low *bcl-2* levels, i.e., the presence of the conjugate inside the cells indicates over-expression of the *bcl-2* transcript therefore a pathological state that is cancer (claims 41, 42, 48-52, and 80) (p. 1178, column 2 bridging p. 1179). Lewis et al. do not teach a targeting moiety capable of binding to a

cell surface molecule (claim 1). Liang et al. teach enhancing therapeutic delivery to cells by receptor-mediated endocytosis (Abstract, p. 236, column 2). Liang et al. teach conjugation of transferring to a PNA capable of binding to plasmid DNA, wherein conjugation is via a disulfide bond linkage and wherein the conjugate is used to deliver plasmid DNA to the transferrin receptor on cell surface (p. 239, columns 1 and 2, p. 240, columns 1 and 2). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the compound of Lewis et al. by replacing their peptide with the transferring of Liang et al., with a reasonable expectation of success. The motivation to do so is provided by Liang et al., who teach the utility of using receptor ligands for enhanced delivery of therapeutics to specific sites via receptor-mediated endocytosis (p. 241, column 1, second paragraph, p. 242, column 2, second paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such compositions can be successfully made and used. With respect to the limitation recited in claim 28, PNAs comprise N-ethylaminoglycine backbone units and the bases are covalently bound to the backbone by methylene-carbonyl units (see Basu et al.). With respect to the limitation of pharmaceutical composition, the transfection buffer (i.e., a pharmaceutically acceptable carrier) comprising the conjugate is a pharmaceutical composition. With respect to the linkers recited in claim 3, absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results.

Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

14. Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 80, 82, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., as applied to claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 above, in further view of Nakano et al. (2001, cited on form PTO-892 on 05/16/2006).

Lewis et al. taken with Liang et al. and Basu et al. do not teach K-RAS (claims 33 and 82). Nakano et al. teach gene transfer antisense K-*ras* as a therapeutic agent for cancer (Abstract, p. 492, column 1, last paragraph, p. 493 bridging p. 495). It would have been obvious to one of skill in the art, at the time the invention was made, to use the compound taught by Lewis et al. taken with Liang et al. and Basu et al., wherein the PNA is directed against K-*ras* to deliver diagnostic and therapeutic agents to cancer cells such as colon and pancreatic cancer cells that are known to over-express K-*ras*, with a reasonable expectation of success. Such a delivery of a diagnostic agent would result in detecting the over-expression of K-*ras* transcript inside these cells. One of skill in the art would have been motivated to do so because Nakano et al. teach that K-*ras* is ove-expressed in many cancer cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the successful

use of such methods. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

15. Claims 1, 3, 4, 28-32, 34, 41-45, 48-52, 69, 71-73, 80, 83, 85, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., as applied to claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 80, 83, 85, and 86 above, in further view of Tomalia et al.

Lewis et al. taken with Liang et al. and Basu et al. do not teach a dendrimer (claim 43) or a plurality of chelants optionally complexed to one or more diagnostic metal ions (claims 44 and 45). Tomalia et al. teach that PNA can be conjugated to dendrimers or a plurality of denrimers, i.e., a plurality of chelants (column 3, lines 22-40, column 13, lines 5-11, column 41, lines 28-34, column 45, lines 1-9, column 47, lines 1-10) for delivery of diagnostic compounds, such as Gd(III) into cells. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al. taken with Liang et al. and Basu et al. by using Gd(III) chelated to one or multiple dendrimers, as taught by Tomalia et al., with a reasonable expectation of success. The motivation to use dendrimers is provided by Tomalia et al., who teach dendrimers as being very efficient in delivering agents to cells. The motivation to use a plurality of chelants is also provided by Tomalia et al., who teach that such compounds can be used to deliver multiple agents to cells. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches the

successful maker and use of such compositions. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER